REMARKS

The Applicants thank the Examiner for the thorough examination of the application. The specification has been amended to improve the format and enumeration of the Tables. It is believed that no new matter is added to the application by this amendment.

Status Of The Claims

Claims 22-43 are pending in the application. Claims 1-21 are cancelled. Claims 22-43 correspond to cancelled claims 1-21. Claim 22 also finds support at page 4, line 23 of the specification.

Objection To The Specification

The Examiner objects to the specification as failing to include subject headings and as incorrectly numbering the Tables. The specification has been amended to add subject headings to the relevant sections and to enumerate the Tables in proper sequence.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-21 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Applicants respectfully traverse.

Claims 1-21 have been cancelled and are replaced by claims 22-43. Claims 22-43 are free from informalities arising from lack of articles at the beginning of a

claim, conditional language, insufficient antecedent basis, and terms such as "suitable" and "such as." Claims 22-43 also do not recite a broader limitation together with a narrower limitation. Claims 22-43 further do not omit essential elements.

The claims are therefore clear, definite and have full antecedent basis. This rejection is accordingly overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §102(b) Over Zuckermann et al.

Claims 1-17 and 21 are rejected under 35 U.S.C. §102(b) as being anticipated by Zuckermann et al. (Proc. Natl. Acad. Sci., 1992). Applicants traverse.

Zuckermann et al. pertains to the identification of highest affinity ligands by affinity selection from equimolar peptide mixtures generated by robotic synthesis. In describing the components of the peptide libraries to be screened, Zuckermann et al. at page 4505, column 2, lines 6-8 states: "The components of these libraries are synthesized in ***equimolar*** proportions by physically separating the solid support . . ." (Emphasis added).

In contrast, independent claim 22 of the invention sets forth "isolating and/or identifying at least one active chemical substance from a ***non-equimolar*** mixture of active or inactive chemical substances . . ." Zuckermann et al. therefore clearly fails to disclose or suggest the invention as set forth in claim 22. Claims depending upon claim 22 are patentable for at least the above reasons.

This rejection is overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §102(b) Over van Breemen et al.

Claims 1-12, 16, 17 and 21 are rejected under 35 U.S.C. §102(b) as being anticipated by van Breemen et al. (Anal. Chem., 1997) Applicants traverse.

Van Breemen et al. pertains to pulsed ultrafiltration mass spectrometry for the screening of combinatorial libraries. Van Breemen et al. fails to disclose ore suggest non-equimolar screening.

Van Breemen et al. at page 2160, column 2, line 23 describes an "***equimolar*** library of 19 adenosine analogs." Van Breemen et al. at page 2160, column 2, lines 44-46 describe "an ***equimolar*** (0.04 μM) mixture of ascorbic acid, salicylate, thyroxine, tryptophan, and warfarin." (Emphases added).

In contrast, independent claim 22 of the invention sets forth "isolating and/or identifying at least one active chemical substance from a ***non-equimolar*** mixture of active or inactive chemical substances . . ." (Emphasis added). Van Breemen et al. therefore clearly fails to disclose or suggest the invention as set forth in claim 22. Claims depending upon claim 22 are patentable for at least the above reasons.

This rejection is overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §102(b) Wieboldt et al.

Claims 1-12, 16, 17 and 21 are rejected under 35 U.S.C. §102(b) as being anticipated by Wieboldt et al. (Anal. Chem., 1997). Applicants traverse.

Wieboldt et al. pertains to immunoaffinity ultrafiltration with ion spray HPLC/MS for screening small molecule libraries. Wieboldt et al. fails to disclose or suggest non-equimolar screening.

In the "Experimental Section" of Wieboldt et al. at page 1684, right column, lines 24-25, the concentration of each of the compounds to be screened in the mixture was 10 μM. As a result, Wieboldt et al. clearly uses equimolar concentrations.

In contrast, independent claim 22 of the invention sets forth "isolating and/or identifying at least one active chemical substance from a ***non-equimolar*** mixture of active or inactive chemical substances . . ." (Emphasis added). Wieboldt et al. therefore clearly fails to disclose or suggest the invention as set forth in claim 22. Claims depending upon claim 22 are patentable for at least the above reasons.

This rejection is overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §103(a) Over Zuckermann et al., van Breeman et al. or Wieboldt et al. In View Of Kunihiro et al.

Claim 18 (which pertained to thrombin, see instant claim 43) is rejected under 35 U.S.C. §103(a) Over Zuckermann et al., van Breeman et al. or Wieboldt et al. in view Of Kunihiro et al. (U.S. Patent 5,300,490). Applicants traverse.

The failures of Zuckermann et al., van Breeman et al. or Wieboldt et al. to disclose or suggest a non-equimolar technology has been discussed above. Kunihiro et al. fails to address the deficiencies of these references.

Kunihiro et al. pertains to a method of binding very big molecules from a natural solution (urine) to the very much smaller molecule thrombin. In Kunihiro et al., thrombin must be distributed on the surface on an anion-exchange resin or order to be able to bind the large thrombomodulin-like molecules. These teachings of Kunihiro et al. fail to be comparable to the present invention, where the thrombin molecule is "fishing" in a solution for smaller ligands to form a complex that can be separated from the solution.

The inventors have observed that in the present invention, the ligands are being bound in a three-dimensional way to the bigger (in this case) target thrombin (as well as to trypsin, β-adrenoreceptor and other target molecules). In contrast, the affinity chromatography of Kunihiro et al. accomplishes two-dimensional binding distributed over a large surface.

Therefore, Kunihiro et al. fails to address the deficiencies of the primary references in teaching or suggesting non-equimolar technology. Also, one of ordinary skill in the art would fail to be motivated by Kunihiro combined with Zuckermann et al., van Breeman et al. or Wieboldt et al. the produce a technology that "fishes" ligands from non-equimolar mixtures. A *prima facie* case of obviousness has thus not been made.

This rejection is overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §103(a) Over Zuckermann et al., van Breeman et al. or Wieboldt et al. In View Of Kurome et al.

Claim 19 (which pertained to trypsin, see instant claim 43) is rejected under 35 U.S.C. §103(a) Over Zuckermann et al., van Breeman et al. or Wieboldt et al. in view Of Kurome et al. (U.S. Patent 5,824,503). Applicants traverse.

The failures of Zuckermann et al., van Breeman et al. or Wieboldt et al. to disclose or suggest a non-equimolar technology has been discussed above. Kurome et al. fails to address the deficiencies of these references.

Kurome et al. pertains to gene encoding endoglycoceramidase activator. In Kurome et al., trypsin is only disclosed as a digesting means for endoglycoceramidase activator II (see Kurome at al. at column 18, lines 37-39 and 44 - Example 3). Kurome et al. therefore has no disclosure or suggestion of using trypsin for the purpose of binding molecules.

Therefore, Kurome et al. fails to address the deficiencies of the primary references in teaching or suggesting non-equimolar technology. Also, one of ordinary skill in the art would fail to be motivated by Kurome combined with Zuckermann et al., van Breeman et al. or Wieboldt et al. the produce a technology that uses trypsin to bind molecules. A *prima facie* case of obviousness has thus not been made.

This rejection is overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §103(a) Over Zuckermann et al., van Breeman et al. or Wieboldt et al. In View Of Soppet et al.

Claim 20 (which pertained to β-adrenoreceptor, see instant claim 43) is rejected under 35 U.S.C. §103(a) Over Zuckermann et al., van Breeman et al. or Wieboldt et al. in view Of Soppet et al. (U.S. Patent 6,338,951). Applicants traverse.

The failures of Zuckermann et al., van Breeman et al. or Wieboldt et al. to disclose or suggest a non-equimolar technology has been discussed above. Soppet et al. fails to address the deficiencies of these references.

The Examiner turns to Soppet et al. for teachings pertaining to β-adrenoreceptor.

Soppet et al. pertains to G-protein parathyroid hormone receptor HLTDG74. Soppet et al. at column 11, lines 7-10 states: "The G-protein PTH receptors of the present invention may be employed in a process for screening for compounds which activate (agonists) or inhibit activation (antagonists) of the receptor polypeptide of the present invention." Soppet et al. at column 11, lines 17-19 states: "The expressed receptor is then contacted with a test compound to observe binding, stimulation or inhibition of a functional response." The process for screening is thus only stated in a general way.

However Soppet et al. discusses that the process includes the use of cells at column 11, lines 34-38, with which a compound to be screened are contacted (see also PCT WO 92/01810, referred to in Soppet et al. at column 11, line 24). One

can then observe whether such a compound generates a signal, i.e., activates the receptor.

Therefore, Soppet et al. fails to address the deficiencies of the primary references in teaching or suggesting non-equimolar technology. Also, one of ordinary skill in the art would fail to be motivated by Soppet et al. combined with Zuckermann et al., van Breeman et al. or Wieboldt et al. the produce a technology that uses β-adrenoreceptor to bind molecules in a search with a mixture of chemical substances to form a complex with the target, which is ten separated, and from which one or more chemical substances are then liberated. That is , the inventive screening process using β-adrenoreceptor is not suggested by Soppet et al. combined with Zuckermann et al., van Breeman et al. or Wieboldt et al. A *prima facie* case of obviousness has thus not been made.

This rejection is overcome and withdrawal thereof is respectfully requested.

Drawings

The Examiner is respectfully requested to indicate whether the drawing figures are acceptable in next official action.

Foreign Priority

The Examiner has acknowledged foreign priority in the Office Action mailed October 6, 2004.

Information Disclosure Statements

The Examiner is thanked for considering the Information Disclosure Statements filed March 22, 2002, June 24, 2002 and August 19, 2002, and for making the initialed PTO-1449 forms of record in the application in the Office Action mailed October 6, 2004

Conclusion

The Examiner objections and rejections have been overcome, obviated or rendered moot. No issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Robert E. Goozner, Ph.D. (Reg. No. 42,593) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $450.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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